Asthmatic Granulomatosis

A Novel Disease with Asthmatic and Granulomatous Features

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***Rationale*: Severe asthma represents 5–10% of all asthma, yet remains problematic and poorly understood. Although it is increasingly recognized as consisting of numerous heterogenous phenotypes, their immunopathology, particularly in the distal airways and interstitium, remains poorly described.**

***Objectives*: To identify the pathobiology of atypical difficult asthma.**

***Methods*: We report 10 from a total of 19 patients (17 women and 2 men) meeting asthma and severe asthma definitions, requiring daily systemic corticosteroid (CS) use, with inconsistent abnormalities on chest computed tomography scans, who underwent video-assisted thoracoscopic biopsies for further diagnosis and management.**

***Measurements and Main Results*: The pathology of 10 of the 19 cases revealed small airway changes consistent with asthma (eosinophilia, goblet cell hyperplasia), but with the unexpected finding of interstitial nonnecrotizing granulomas. These patients had no evidence for hypersensitivity pneumonitis, but 70% of cases had a personal or family history of autoimmune-like disease. The 10 cases were treated with azathioprine, mycophenolic acid, methotrexate, or infliximab. Nine of 10 showed decreased CS requirements and improved or maintained FEV_1 despite lower CS doses. Of the remaining nine patients, six manifested asthmatic small airway disease, alone or in combination with alveolar septal mononuclear cells, but no granulomas, whereas three manifested other pathologic findings (aspiration, pneumonia, or thromboemboli).**

***Conclusions*: These data suggest that a subset of severe "asthma" manifests a granulomatous pathology, which we term "asthmatic granulomatosis." Although identification of this disease currently requires a thorascopic biopsy, alternative approaches to therapy lead to improvement in outcomes.**

Keywords: asthma; hypersensitivity pneumonitis; granulomas; eosinophils; autoimmunity

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Diseases with reversible airflow limitation are traditionally grouped together under the term "asthma." However, many of these patients can have atypical features, including later age at onset and low diffusing capacities. Very little is understood regarding the pathobiology of these atypical patients.

What This Study Adds to the Field

We present video-assisted thoracoscopic biopsy findings from 10 patients, previously diagnosed with severe asthma and meeting criteria for asthma. Pathobiologically, these patients have evidence for asthmatic small airway inflammation and infrequent nonnecrotizing granulomas with interstitial inflammation. This distinct pathobiology in addition to their response to cytotoxic agents suggests that these patients represent a newly described disease, which we term asthmatic granulomatosis.

The term "asthma" has been loosely defined as the presence of appropriate symptoms in the setting of airway hyperresponsiveness or reversible airflow limitation, requirements met by a broad range of patients (1). Cohort studies in asthma and severe asthma are now uniformly identifying different subtypes or phenotypes that thus far differ by degree of airflow limitation, inflammatory or allergic processes, and age at onset (2–4). These phenotypes are perhaps best differentiated in patients identified with "severe asthma," a grouping of patients again defined clinically and physiologically (4–6). The pathology behind these different phenotypes is poorly understood.

Pathologic studies of severe asthma are generally limited to small bronchoscopically obtained partial-thickness large airway biopsies, which do not include smaller airways or alveolated parenchyma. Although transbronchial and distal lung biopsies have been obtained they are not without risk, and the amount of small airway tissue obtained is limited (7, 8). Most descriptions of distal lung pathology in asthma are from autopsies of fatal asthma exacerbations, with additional rare descriptions of pathology in lobes resected for tumors, where clinical and physiologic details are lacking (9–12). This contrasts with studies of interstitial lung disease where large-volume lung biopsies, often driven by radiologic abnormalities on computed tomography (CT) scans, have served to identify pathologic subtypes. Thus, for nearly all presentations of severe forms of asthma, limited pathologic data are available that could inform phenotypes, mechanisms, and therapies.

The University of Pittsburgh and University of Pittsburgh Medical Center operate a Difficult Asthma Clinic that receives referrals of patients with difficult asthma locally, regionally, and

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nationally. Despite patients receiving an extensive evaluation and optimization of treatment, many of these patients remain poorly controlled. We suspected that larger-volume lung tissue biopsies obtained through video-assisted thorascopic surgery (VATS) could identify novel histopathologies with distinct immunoinflammatory elements to suggest new approaches to therapy. We report 10 adult patients, all previously diagnosed with severe asthma, whose lung tissue revealed small airway disease in association with poorly formed nonnecrotizing interstitial granulomas. In addition to their clinical, inflammatory, and physiologic characteristics, we report their improvement with alternative nonsteroidal antiinflammatory drugs. Some of these results have previously been reported in abstracts (13, 14).

METHODS

Evaluation

Patients were referred for evaluation of severe corticosteroid (CS) refractory asthma to the Difficult Asthma Clinic at the Comprehensive Lung Center of the University of Pittsburgh Medical Center. Asthma was defined using American Thoracic Society criteria and severe asthma defined by the American Thoracic Society workshop definition, including use of high-dose inhaled (>880 μg fluticasone or equivalent) or systemic CSs with at least two of seven minor criteria (1, 5). All received a standardized evaluation, with extensive history and physical examination; pulmonary function testing with bronchodilator reversibility to 720 μg of inhaled albuterol using an Aerochamber (Monaghan, Plattsburgh, NY); diffusing capacity of carbon monoxide (D_{LCO}); chest CT and in some cases high-resolution CT (HRCT); IgE and specific IgE/allergen skin testing; complete blood count; and evaluation of CS side effects. Most patients had measurement of exhaled nitric oxide (F_{ENO}), C-reactive protein, antinuclear antigen, rheumatoid factor, screening precipitins for hypersensitivity pneumonitis (HSP), quantitative immunoglobulins, and sinus CT scans. They were asked questions on age at asthma onset, use and adherence to CSs, existence of other chronic diseases including sinusitis, environmental exposures, and family history of allergic and autoimmune diseases. All met with a certified asthma educator. Patients were assessed for 3–24 months to optimize asthma therapy and to better understand their disease, its variability, and need for systemic CSs. All CT scans were overread for this study by a chest radiologist (D.C.S.). Approximately 170 unique patients with severe asthma have been followed in the Difficult Asthma Clinic from 2007 to 2011.

Thoracoscopic Biopsy

Nineteen patients with severe asthma with CT scans without parenchymal abnormalities and atypical asthma presentations (low D_{LCO}), adult onset, persistent eosinophilia, or very low forced expiratory flow midexpiratory phase ($FEF_{25–75\%}$ predicted) who did not improve or worsened over time were recommended for VATS biopsies. Most of the surgeries were performed by a single surgeon (M.S.). Because these patients had no localized or parenchymal radiologic abnormalities by chest CT, multiple random biopsies were taken from each lobe of a single lung. Double-lumen endotracheal intubation with single-lung ventilation was used for all patients. Care was taken to ensure that generous wedge resections were done to include deep tissue. Tissue samples were sent for culture (all negative for bacteria, fungus, and mycobacteria) and pathologic analysis. Initially, patients gave consent using general lung tissue repository consent. However, since 2010, consent was obtained using an airway disease–specific consent to collect lung tissue for future research protocols and to allow use of clinical, physiologic, radiologic, and immunoinflammatory data. The protocols and consents were approved by the University of Pittsburgh Institutional Review Board.

Pathologic Analysis

All biopsies were entirely processed in formalin; embedded in paraffin; and stained with hematoxylin and eosin, Verhoeff-van Gieson, acid-fast, and Gomori methenamine silver stains. Immunohistochemistry for L26/CD20, CD3, CD4, CD8, Beta F1, TIA, CD79, CD138, S100 protein, Langerin, and mast cell tryptase were performed as previously described (15). The ratio of CD4 to CD8 cells was calculated by manually counting the number of T cells in three identical fields adjacent to the small airways (16).

Follow-up

Seventeen of the 19 patients were offered treatment with alternative antiinflammatory or cytotoxic medications: azathioprine (Imuran), methotrexate, or anti–tumor necrosis factor-α (Remicade). Treatment with these antiinflammatory medications was instituted for 3 months and continued for 12–48 months if response was seen. Treatment was stopped if ineffective or poorly tolerated. A patient was considered a "responder" to alternative therapy if he or she (*1*) was able to reduce his or her prednisone dose to 5 mg or less, (*2*) maintained or improved their FEV_1 % predicted despite lower oral CS doses, and (*3*) had one or fewer oral CS-requiring exacerbations during the year following. Patients were monitored monthly with complete blood counts, liver function, and pulmonary function tests.

RESULTS

Demographics and Clinical Characteristics

Demographics and clinical characteristics are presented in Table 1. Ten of the 19 patients with a clinical diagnosis of severe asthma who underwent VATS biopsy between 2007 and 2011 had a combination of asthmatic small airway changes with nonnecrotizing interstitial and airway-centric granulomas on pathology. All

TABLE 1. DEMOGRAPHICS AND LUNG FUNCTION BY INDIVIDUAL PATIENT

Patient	Age	Age at Onset	FEV_1 %	FEV/FVC	$FEF_{25–75\%}$	% Bronchodilator Response*	D_{LCO}
#1	49	29	63	60	28	15/9	78
#2	60	5	56	82	53	13/61	56
#3	59	23	84	74	52	22/50†	68
#4	62	50	57	63	27	12/19	57
#5	36	30	39	42	10	12/16	108
#6	52	45	73	78	46	5/4	75
#7	30	5	86	72	58	1/−6‡	62
#8	55	5	69	69	36	20/35	67
#9	63	60	97	62	32	−4/−2†	95
#10	56	28	45	52	16	19/73	96
Mean ± SD or SEM	52 ± 11	28 ± 20	66 ± 6	65 ± 4	36 ± 5	12 ± 3 and 26 ± 9	76 ± 6

Definition of abbreviations: D_{LCO} = diffusing capacity of carbon monoxide; $FEF_{25–75\%}$ = forced expiratory flow, midexpiratory phase.

* % BD response for $FEV_1/FEF_{25–75}$.

† Positive methacholine challenge PC20 = 3.6 mg/ml (#3), 0.4 mg/ml (#9).

‡ Patient with greater than 12% reversibility to prednisone.

TABLE 2. IMMUNOINFLAMMATORY AND RADIOLOGIC FEATURES

Patient	Blood (*eos/ml*)	IgE (*IU/ml*)	Atopy (*Y/N*)	F_{ENO} (*ppb*)	CRP	Sinus CT	Chest CT
#1	780	5	No	10	0.7	ND	Normal
#2	100	15	No	19		Normal	Normal
#3	1,800	72	Yes	113	0.4	Polyps/sinusitis	Bronchial wall thickening
#4	200	7	Yes	57	0.34	Pansinusitis	Normal
#5	200	16	Yes	10	0.39	Mild sinusitis	Air trapping
#6	100	280	Yes	22	3.5	Sinusitis	Mosaicism
#7	200	19	No	88	0.25	Mild sinusitis	Normal
#8	350	630	Yes	39	0.83	Mild thickening	Normal
#9	1,390	99	No	58	5.6	Sinusitis/polyps	Air trapping
#10	300	166	Yes		14.3	Mild thickening	Bronchial dilatation
Median (25th–75th percentiles)	325 (200–760)	54 (15–252)	6/4	42 (15–79)	0.8 (0.4–4)		

Definition of abbreviations: CRP = C-reactive protein; CT = computed tomography; F_{ENO} = exhaled nitric oxide.

patients had been diagnosed with severe asthma by referring physicians, were oral CS dependent (5–60 mg/day), and had no evidence for other respiratory disease. One patient was on omalizumab, none on methotrexate. All patients were white, 9 of 10 were female, and 8 of 10 were middle-aged. The cases were referred from western Pennsylvania, upstate New York, and Maryland. Most were diagnosed with asthma as adults and all had a history of sinus disease (*see* Figure E1 in the online supplement). The patients were all currently symptomatic with cough, wheeze, chest tightness, and shortness of breath. There was no history of untreated and symptomatic gastroesophageal reflux or aspiration, whereas 1 of 10 reported aspirin-exacerbated respiratory disease. All were treated with traditional asthma medications, including inhaled CSs, long-acting β-agonists and, leukotriene modifiers. Nocturnal awakenings were not common. Three or more exacerbations in the previous year were common and often triggered by worsening sinus disease. All smoked less than 10 pack-years and none had smoked in the last year. Although wheezing was common, no crackles were heard on examination.

Physiologic, Radiologic, and Immunologic Findings

Physiologic, radiologic, and immunologic findings are presented in Table 2. All 10 cases had evidence of airflow limitation, reversibility, and in two cases a provocative concentration of methacholine less than 8 mg/ml despite high-dose inhaled and systemic CSs. The $FEF_{25–75\%}$ predicted was disproportionately low compared with the FEV_1 % predicted and FEV_1/FVC. Unlike traditional asthma, the D_{LCO} was modestly reduced in most cases (76 ± 6 % predicted).

All patients had a chest CT performed within 10 months of surgery. Images were reconstructed at 5 (n = 9) or 2.5 mm (n = 1) during inspiration. In some cases, 1.25-mm thin HRCT images (n = 4), 0.625-mm source images (n = 10), or chest CT performed during end-expiration (n = 1) were available for review. One or more comparison chest CTs, to include expiratory CT (n = 1), were available in six cases. Five patients had a normal CT. The other five CTs revealed nonspecific findings of bronchiolar dilation (n = 5); bronchiolar wall thickening (n = 4); patchy predominantly subsegmental air trapping (n = 2); subsegmental atelectasis (n = 2); tree-in-bud opacities (n = 1); or small mucosal nodules in the central airways (n = 1) (*see* Figure E2). Focal or extensive bronchiectasis, thoracic lymph node enlargement, and consolidation were absent.

Peripheral blood eosinophilia was present in most and high F_{ENO} despite systemic CSs. There were no consistent or suggestive environmental exposures, the IgE was not consistently elevated, and precipitating antibody screens for HSP were negative. Although IgG levels were occasionally low (likely on the basis of chronic systemic CS use), pre- and posttetanus and pneumococcal pneumonia vaccination titer responses were normal. Atopy was present in 6 of 10. Nine of 10 had significant sinus disease by CT scan, with 5 of 10 having a history of sinus surgery. Of the 10 patients, 60% had a family history of autoimmune disease: rheumatoid arthritis (two); Crohn disease (one); mixed connective tissue disease (one); CRST syndrome (one); and dermatomyositis (one). Two patients had a personal

TABLE 3. HISTOPATHOLOGIC FEATURES OF TEN CASES OF ASTHMATIC GRANULOMATOSIS

Small airways	
Submucosal inflammation	10/10
Eosinophils	7/10
Neutrophils	2/10
Lymphocytic transmigration	8/10
Submucosal fibrosis	6/10
Mucus plugging	8/10
Peribronchiolar fibrosis	6/10
Bronchiolectasis	6/10
Muscular hypertrophy	10/10
Interstitial mononuclear pneumonia	
Granulomas	10/10
Airspace organization	5/10
Lymphoid aggregates	4/10

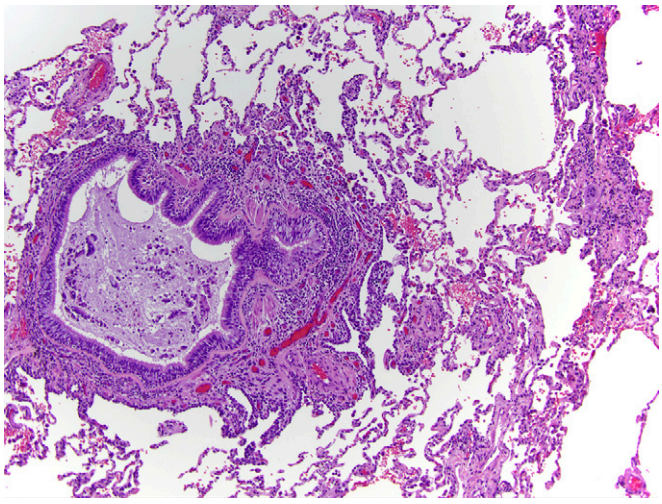

Figure 1. Asthmatic granulomatosis. The small airways are occluded by large mucus plugs containing eosinophils with the submucosa expanded by a chronic inflammatory cell infiltrate. A patchy interstitial mononuclear infiltrate with poorly formed granulomas is also noted (*at right*) (hematoxylin and eosin, ×100).

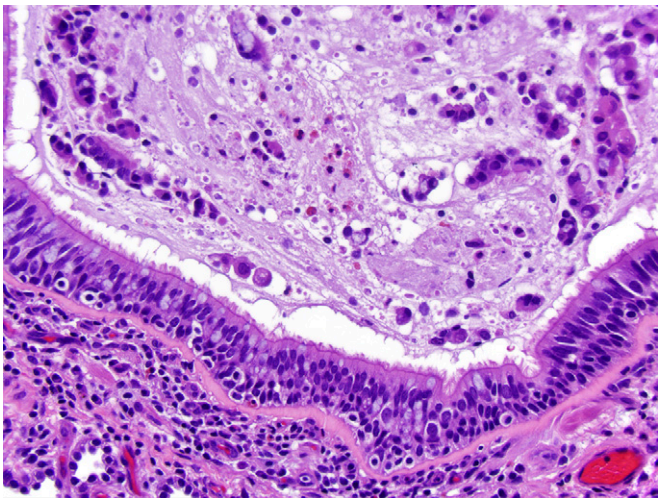

Figure 2. Asthmatic granulomatosis. Mucus plugs within the airways contain degenerating eosinophils, whereas the bronchiolar epithelium shows goblet cell metaplasia, basement membrane thickening, and a mixed submucosal infiltrate with eosinophils (hematoxylin and eosin, ×200).

history of autoimmune disease (psoriasis and inactive Crohn disease by recent colonic biopsy).

Pathologic Analysis

Multiple unilateral wedge biopsies from the right (three) or left (two) lung were taken from all patients. The histopathology of the 10 cases is detailed in Table 3. Histologic changes consisted of an asthmatic bronchiolitis accompanied by a patchy interstitial infiltrate of alveolar septal mononuclear cells with poorly formed nonnecrotizing granulomas in all 10 (Figure 1). Terminal bronchioles displayed papillary epithelial hyperplasia, basal cell hyperplasia, and goblet cell metaplasia in all cases (Figure 2). Mucous plugging was noted in 8 of the 10 cases (80%) as was a mild bronchiolectasia in 60%. Subepithelial basement membrane thickening, consistent with asthma, was seen in all cases but was pronounced in five (Figure 2). A mild to moderate submucosal chronic inflammatory cell infiltrate was noted in all cases, with epithelial transmigration in eight. Eosinophils were easily identified in 70% of biopsies (Figures 2 and 3) and plasmacytoid lymphocytes and plasma cells were present in aggregates in 60%. Patchy submucosal and peribronchiolar fibrosis was noted in most cases and muscular hypertrophy of the bronchiolar muscularis was ubiquitous, but dramatic in eight instances. No fibrous obliteration or significant compromise of airway lumens was observed.

A patchy interstitial mononuclear infiltrate associated with the airway changes was localized primarily to the perivenular regions and alveolar septa, accompanied by airspace fibrin and granulation tissue in 50%. Ill-defined, nonnecrotizing granulomas comprised of epithelioid histiocyte aggregates with or without giant cells were noted in all 10 cases, but were relatively infrequent (Figures 3, 4, and 5). Interstitial lymphoid aggregates were seen in four cases.

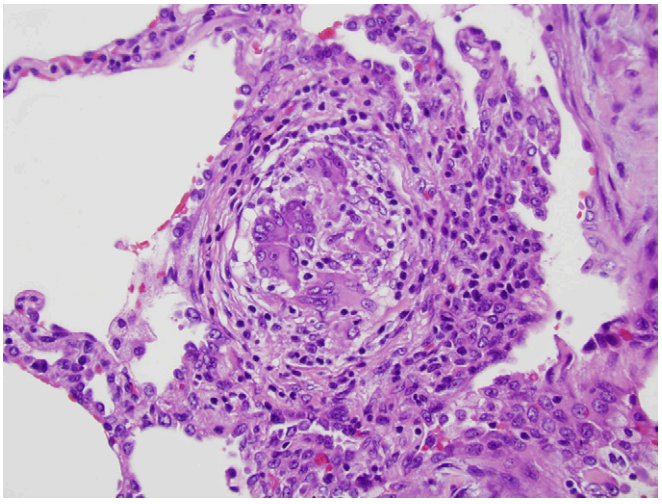

Figure 4. Asthmatic granulomatosis. A granuloma is seen within the interstitium (hematoxylin and eosin, ×400).

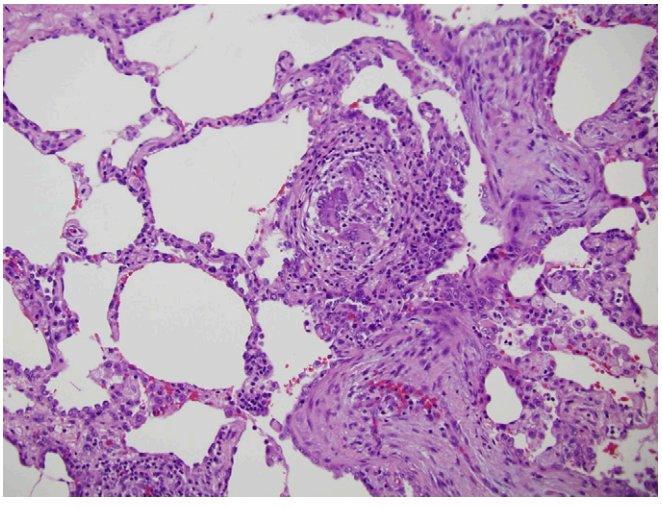

Figure 3. Asthmatic granulomatosis. Small airway changes were associated with a patchy alveolar septal mononuclear infiltrate with airspace granulation tissue and interstitial nonnecrotizing granulomas and loose aggregates of giant cells and epithelioid histiocytes (hematoxylin and eosin, ×200).

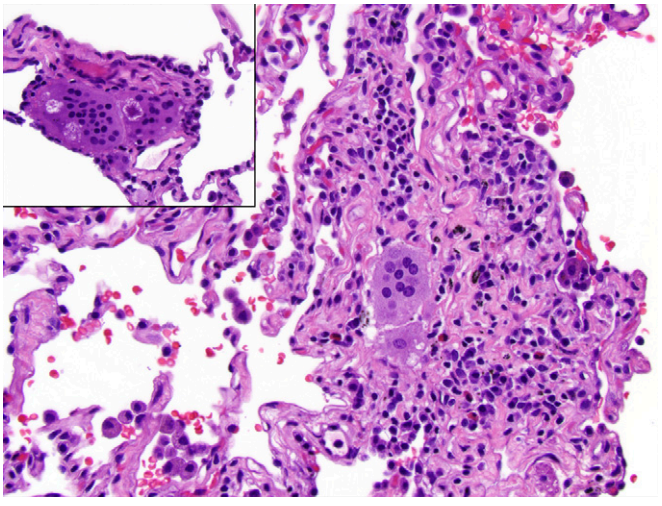

Figure 5. Asthmatic granulomatosis. A patchy mononuclear infiltrate with interstitial and bronchiolocentric poorly formed granulomas containing giant cells, epithelioid histiocytes, and occasional asteroid bodies (*inset*) is common (hematoxylin and eosin, ×200; inset, hematoxylin and eosin, ×400).

Immunohistochemical analysis revealed most inflammatory cells to be Beta F1 CD3 positive T cells with a CD4/CD8 ratio of 4.2 (range, 2.8–5.1), with most intraepithelial lymphocytes a Beta F1 CD3/CD4 positive, TIA-negative phenotype. L26/CD20 stains highlighted lymphoid aggregates and scattered submucosal B cells, whereas CD79A and CD138 studies showed plasmacytoid lymphocytes and plasma cells in aggregates in the submucosa of those cases with the most prominent inflammatory infiltrates. S100 protein and Langerin stains displayed rare intraepithelial and submucosal Langerhans cells, whereas mast cell tryptase staining showed nonaggregated and scattered mast cells throughout the interstitium.

There was no evidence for microorganisms by silver and acid-fast stains, vasculitis, necrosis, fibroblastic foci, honeycomb change, or aspirated material.

Additional Surgical Cases

The remaining nine cases (*see* Tables E1 and E2 for clinical and immunoinflammatory details) included one aspiration (food particles in the airways); one eosinophilic airway inflammation with superimposed acute pneumonia; and one case with marked thromboembollic disease in the presence of asthmatic and respiratory bronchiolitis and interstitial granulomas (15 pack-year smoking history). Two patients manifested eosinophilic small airway disease and alveolar septal mononuclear cell infiltrates without granulomas, whereas four manifested only small airway disease consisting of goblet cell hyperplasia and mixed submucosal eosinophilic/mononuclear inflammation. In these six patients, small airway inflammatory changes were similar to the 10 cases. In several cases, low D_{LCO}, low $FEF_{25–75\%}$ predicted, high blood eosinophils, and high F_{ENO}s were observed.

Asthma Control Subjects

Seventeen deidentified autopsies of adult patients (nine women and eight men; median age, 58; range, 26–76) admitted with a known diagnosis of inactive chronic but well-controlled asthma who died of nonpulmonary causes were reviewed as a control group. Although changes of asthmatic bronchitis and bronchiolitis were seen, no granulomas were identified. A patchy inconspicuous interstitial infiltrate of mononuclear cells was seen in 35% of patients.

Response to Therapy

All 10 cases were treated with oral CSs ranging from 5 to 60 mg/day and had been CS dependent for as long as 20 years. Of the 10, six patients on azathioprine, one on methotrexate (intramuscular), one on infliximab, and one on mycophenolic acid have successfully reduced their systemic CS dose to 5 mg per day (Table 4). Although azathioprine is the first drug used (and most successful), it is not always well tolerated, because three discontinued for nausea and one for liver function test abnormalities. One patient has not been able to tolerate any alternative therapy to date and therefore response cannot be evaluated. The nine responders have had improvements in FEV_1, FVC, and $FEF_{25–75}$, in their level of symptoms and activity despite lower (or stable) CS doses. Despite frequent CS burst pre-VATS, no responding patient has required more than one CS burst per year after response to therapy. In three patients treated for more than 1 year, attempts to taper azathioprine have been unsuccessful, leading to worsening clinical symptoms, worsening airway obstruction, and increased CS doses. When the azathioprine dose was increased back to 250–300 mg per day, the symptomatology and lung function returned to the prereduction baseline.

Responses to Therapy in the Nine Additional Cases

Table E3 shows responses to therapy in the nine additional cases. One patient (aspiration) was lost to follow-up. In the four patients with small airway disease only, three of four could be characterized as "responders" to azathioprine, whereas one would not (patient #2). Both patients with airway disease and mononuclear septal infiltrates without granulomas have had reductions in oral CS requirements, but mixed improvement in FEV_1 % predicted (one azathioprine, one myophenolic acid [after LFT increases with azathioprine]). The case with thromboembolic disease has been anticoagulated and is under evaluation by rheumatology for recent positive antiphospholipid IgM antibody. The case with eosinophilic inflammation and pneumonia has not responded to any therapy, including anti–IL-5 (mepolizumab).

DISCUSSION

Except for fatal asthma, the distal lung pathology of severe reversible obstructive airway disease (asthma) and its phenotypes remains poorly described. We present thoracoscopic biopsy data from 19 adults, all diagnosed with "severe asthma," 10 of which reveal granulomas in association with more traditional features of asthmatic or eosinophilic airway inflammation. Importantly, preliminary follow-up studies suggest that nonsteroidal cytotoxic or antiinflammatory therapies improve the course of disease, supporting a continuation of this invasive diagnostic approach in selected cases. We believe that these data support the identification of a newly described clinical and pathologic entity, which we propose to name "asthmatic granulomatosis."

All 19 cases described here met physiologic and clinical criteria for asthma: symptoms; reversible airflow limitation (to β_2 agonists or CSs); or airway hyperresponsiveness in the absence of parenchymal abnormalities on HRCT. Interestingly, the one

TABLE 4. RESPONSE TO NONSTEROIDAL CYTOTOXIC/ANTIINFLAMMATORY THERAPY

Patient	Prednisone Pre (*mg/d*)	Prednisone Post (*mg/d*)	FEV_1% Pre-Rx	FEV_1% Post-Rx	Therapy
#1 (R)	10	5	63	71	AZ
#2 (R)	50	5	58	65	AZ
#3 (R)	20	5	84	91	AZ
#4 (R)	10	5	57	65	AZ
#5 (R)	5	5	39	44	AZ failure (nausea) now infliximab
#6 (R)	30	5	73	71	AZ
#7 (PR)	40	5	86	71	AZ failure (nausea) now MTX IM
#8 (R)	5	5	69	80	AZ
#9 (NE)	13	13	97	112	AZ, MP, MTX failures (nausea, LFTs)
#10 (R)	20	5	45	54	AZ failure (nausea)/now MP acid

Definition of abbreviations: AZ = azathioprine; IM = intramuscular; LFT = liver function tests; MP = mycophenolate; MTX = methotrexate; NE = not evaluable because not on any drug for a least 1 month because of side effects; PR = partial clinical responder; R = clinical responder.

patient who did not meet these criteria before diagnosis (patient #6) developed bronchodilator responsiveness after successful treatment with azathioprine. All 19 also met diagnostic criteria for severe asthma, being on daily systemic CSs; high-dose inhaled CS, usually with a long-term controller; having daily symptoms; and averaging three CS bursts in the previous year. Most patients reported either adult-onset disease or worsening in adulthood. VATS biopsies were performed on these patients to determine the presence of a traditional asthma masquerader, such as a limited Churg-Strauss syndrome or constrictive bronchiolitis, and if not present, to better understand the pathobiology of their severe disease such that alternative therapies might be suggested. The biopsies were all done using a deep cone approach to obtain the airways tissue vital to revealing the described pathology. There have been no complications and all have gone home within 3 days of the procedure.

Ten of the 19 cases manifested a combination of three pathologic findings not previously reported together (asthmatic airway inflammation, alveolar septal mononuclear inflammation, and poorly demarcated nonnecrotizing granulomas). Seven of 10 cases either had an elevated F_{ENO} (>30 ppb) or peripheral blood eosinophilia (>300 per milliliter) despite continuous systemic CSs, consistent with an "asthmatic" Th2-like inflammatory process (17–19). Although the accompanying granulomatous process may be suggestive of HSP, these 10 cases have asthmatic small airway changes including goblet cell metaplasia, thick basement membranes, tissue eosinophilia, and marked muscular wall hypertrophy with mucus plugs that are not part of the spectrum of infection, HSP, aspiration, or autoimmune disease. The lack of interstitial or nodular changes on HRCT scan further argues against an HSP diagnosis (20). Crohn disease of the lung is usually seen with active ileocolonic inflammation, whereas patient #9 was asymptomatic with negative colonic biopsies. Other autoimmune diseases, such as Sjögren and rheumatoid arthritis, and sarcoidosis may have granulomas but lack the asthmatic reactive airway pathology described here. No vasculitis was noted in any case excluding granulomatosis with polyangitis (Wegener's) and Churg-Strauss syndrome. Thus, although we acknowledge the histologic (and clinical) differential diagnoses that need to be considered, it seems that the clinicopathologic profile in these 10 cases is best encompassed in the term "asthmatic granulomatosis," reflecting the asthmatic small airway changes and the granulomatous disease processes.

These three inflammatory elements were present despite systemic CS use, confirming a profound CS resistance, findings previously noted in endobronchial biopsies and sputum from subgroups of patients with severe asthma (3, 6). Although the mechanisms for the CS-resistant eosinophilic, likely Th2, process remain poorly understood, studies of severe eosinophilic subjects with asthma support a role for the Th2 cytokine IL-5 (21, 22). However, the presence of granulomas suggests the immune process reported here is more complex than Th2 alone including elements of innate, Th1, or Th17 immunity, all of which have been identified with granulomatous inflammation (23–25). These processes may be accompanied by IL-8 or interferon-γ, which have been identified with granulomatous inflammation in endobronchial bioposies and sputum from subgroups of patients with severe asthma such as those with eosinophilic pneumonia, and which could contribute to the asthmatic granulomatous histopathology observed here.

Initial characterization of the inflammatory mononuclear cell bronchiolitis in these patients identifies a $CD3^+$ lymphocyte infiltration, predominantly of CD4 cells. Plasmacytoid lymphocytes and plasma cells were present in submucosal lymphoid aggregates in the regions and patients with the most prominent inflammation. Stains for microorganisms and all cultures were negative. This prominence of plasmacytoid and plasma cells might suggest a link to autoimmunity, as does the presence of the nonnecrotizing granulomas themselves. An autoimmune link is further supported by the family or personal history of autoimmunity in 70%.

Although patient #9 had inactive Crohn disease, she reported asthma since childhood, had a high IgE level, and had been treated with anti-IgE therapy with some improvement in symptoms, also supporting an overlap in immune processes. Interestingly, genetic factors, including such genes as SLC22A5 and RORA, which are shared by asthma and Crohn disease, could predispose to granulomatous inflammation, perhaps through modulation of responses to microbial exposures (26).

Four of nine female patients described onset or worsening of their disease during pregnancy, whereas the one man in the dataset is currently treated for low testosterone levels. The Severe Asthma Research Program identified a cluster of women with late-onset disease and an association with hormonal influences (4). Eosinophilic inflammation, as measured in sputum, was prominent, suggesting that at least some of the women described here may have overlap with the predominantly female cluster in the Severe Asthma Research Program. Women in general are predisposed to autoimmune disease, supporting a complex role for hormones in autoimmunity, and perhaps in this newly described asthmatic granulomatosis (27). Although asthma is not thought of as an autoimmune disease (and there were no increases in known autoantibodies), aspirin-exacerbated respiratory disease and, more recently, nasal polyps have been associated with autoantibody formation (28, 29). Indeed, several of the patients described here reported a history of nasal polyps in addition to severe chronic sinusitis.

These 10 patients were accumulated over a 4-year period of time (2007–2011). Although VATS biopsies are not routinely performed in difficult or severe asthma, this novel finding of interstitial granulomas, associated with a clinical response to nonsteroidal medications, suggests this procedure may be justified in a select group of atypical patients, especially given the risks of these immunosuppressive agents. Over the 4 years of the accumulation of these cases, approximately 10% of the 170 patients with severe asthma seen in the Difficult Asthma Clinic underwent VATS biopsy, 50% of whom manifested the unique combination of pathologic findings reported here. Of the remaining nine biopsies, seven manifested one or more of these findings, suggesting that the 10 cases may represent the far end of a spectrum of CS-refractory asthma. Although this pathology and disease are not as common as traditional asthma, over the same period of time, in the same clinic, two cases of allergic bronchopulmonary aspergillosis and only one case of Churg-Strauss syndrome have been identified, suggesting this new pathology or disease is more common than these typical asthma masqueraders.

Of the 10 cases reported here, nine have responded from a moderate to a high degree to cytotoxic and antiinflammatory therapies including azathioprine, methotrexate, anti–tumor necrosis factor-α, and mycophenolic acid. The remaining one has had difficulty tolerating these therapies. Importantly, three responding patients have attempted to taper their azathioprine, but had to return to full or partial dosing because of deterioration in symptoms, increasing steroid requirements, and decline in lung function. In the 1980s, studies inconsistently suggested efficacy of methotrexate in some severe CS-dependent people with asthma (30). No pathology was obtained, but it is conceivable the therapeutic responses observed here may be similar to those noted to methotrexate in the previous reports. Of the six patients who did not manifest all three of the pathologic findings reported here, a more mixed response to immunosuppressive

therapy has been observed. However, four of the six have also been able to markedly decrease their oral CS requirements. This further supports the concept that the range of pathologies reported here may represent varying spectrums of a similar disease. Placebo-controlled trials are necessary to truly determine selective responsiveness of these patients.

In conclusion, we report the unexpected finding of nonnecrotizing granulomas in the airways of 10 patients with clinically and physiologically defined severe asthma. We believe these patients have a newly identified disease, which we name asthmatic granulomatosis. This disease, which overlaps features of asthma, autoimmunity, and granulomatous disease, seemingly responds better to cytotoxic and antiinflammatory agents than to high-dose CSs. We suggest VATS biopsies be considered in atypical CS-dependent patients with severe asthma, especially females who are characterized by adult-onset disease, a family history of autoimmunity, low D_{LCO}, disproportionately low $FEF_{25–75\%}$ predicted with persistent blood eosinophils ($\geqslant$200 per milliliter) and F_{ENO} greater than 30 ppb despite systemic CS use. Further studies are needed to characterize the immunologic pathways involved and to develop biomarkers that would more easily identify and then treat this newly described disease.

Author disclosures are available with the text of this article at www.atsjournals.org.

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